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Correlation of left ventricular systolic dysfunction determined by low ejection fraction and 30-day mortality in patients with severe sepsis and septic shock: A systematic review and meta-analysis☆,☆☆

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ABSTRACT

Introduction: The prognostic implications of myocardial dysfunction in patients with sepsis and its association with mortality are controversial. Several tools have been proposed to evaluate cardiac function in these patients, but their usefulness beyond guiding therapy is unclear. We review the value of echocardiographic estimate of left ventricular ejection fraction (LVEF) in the setting of severe sepsis and/or septic shock and its correlation with 30-day mortality.

Methods: We conducted a systematic review and meta-analysis to evaluate the prognostic functionality of newly diagnosed LV systolic dysfunction by transthoracic echocardiography on critical ill patients admitted to the intensive care unit with severe sepsis or septic shock.

Results: A search of EMBASE and PubMed, Ovide MEDLINE, and Cochrane CENTRAL medical databases yielded 7 studies meeting inclusion criteria reporting on a total of 585 patients. The pooled sensitivity of depressed LVEF for mortality was 52% (95% confidence interval [CI], 29%-73%), and pooled specificity was 63% (95% CI, 53%-71%). Summary receiver operating characteristic curve showed an area under the curve of 0.62 (95% CI, 0.58-0.67). The overall mortality diagnostic odd ratio for septic patients with LV systolic dysfunction was 1.92 (95% CI, 1.27-2.899). Statistical heterogeneity of studies was moderate.

Conclusion: The presence of new LV systolic dysfunction associated with sepsis and defined as low LVEF is neither a sensitive nor a specific predictor of mortality. These findings are limited because of the heterogeneity and underpower of the studies. Further research into this method is warranted.

1. Introduction

Left ventricular (LV) dysfunction associated with sepsis is a phenomenon that has been described decades ago [1] but has gained more recognition recently because of the widespread use of echocardiography in the intensive care unit (ICU) [2,3]. Its mechanism is not clear because of its multifactorial nature and clinical factors including dynamic adaptation of the cardiovascular system to the disease process, host response, and resuscitation [4]. Cellular, extracellular, and molecular mechanisms have been postulated as explanation for myocardial injury such as alterations in coronary blow flow, inflammation, cytokines, or calcium dysregulation [5–7].

Numerous studies have described different types of myocardial dysfunction in sepsis, and a variety of echocardiographic parameters have been developed to assess LV function [8]. Among these parameters, ejection fraction (EF) is most commonly used to evaluate LV systolic function. At present, the most accepted definition of myocardial dysfunction in sepsis is based solely on an LVEF of less than 45% to 50% in the absence of previously diagnosed cardiac disease that demonstrates reversibility upon remission on patients without prior cardiomyopathy [3]. Moreover, the use of more technological advanced methods to evaluate myocardial tissue properties has improved recognition of more subtle myocardial function abnormalities [9,10]. Preliminary data on LV diastolic dysfunction evaluated by tissue Doppler imaging have demonstrated association with mortality; however, the evidence at this point is limited [11,12]. On the contrary, despite larger pooled data, the presence of LV systolic dysfunction and its association to poor outcome remain controversial. Vieillard-Baron et al found that reversible acute LV dysfunction defined as *LV hypokinesis* was not associated with a worse prognosis [13]; however, Furian et al demonstrated a poor prognosis with the presence of LV dysfunction in

Abbreviations: AUC, area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; EF, ejection fraction; FN, false negative; FP, false positive; ICU, intensive care unit; MODS, multiorgan dysfunction syndrome; LR^+, positive likelihood ratio; LR^-, negative likelihood rate; LVEF, left ventricular ejection fraction; LV, left ventricle; SE, standard error; SROC, summary receiver operating characteristic; TN, true negative; TP, true positive; TTE, transthoracic echocardiography.

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this scenario [14]. The presence of low LVEF and its correlation with mortality in sepsis remain unclear [1,13,14]. We conducted a systematic review and meta-analysis to determine whether LV systolic dysfunction associated with sepsis and diagnosed by a low LVEF demonstrated with transthoracic echocardiography (TTE) has a prognostic value in critically ill septic patients.

2. Methods

2.1. Search strategy

We conducted a search of several medical databases including EMBASE and PubMed, Ovid MEDLINE, Cochrane CENTRAL and Web of Science, African Index Medicus, IndMed, Pantelemion, Western Pacific Index Medicus, KoreaMed, LILACS, IMSEAR, and EMRO, with search terms *sepsis or septic*, *Cardiac output or echo* or TTE* and *heart failure, heart disease, or ejection fraction* (see Appendix 1 for full search strategy). References of included and potentially relevant studies were inspected manually for additional studies not identified in the initial database search, including relevant conference proceedings, abstracts, and other "gray literature" sources. The search was limited to clinical studies involving adult human patients admitted to ICUs with septic events. No language or time frame restrictions were applied. Studies were included if there was systematic evaluation of cardiac function in sepsis with reported mortality. Studies were excluded if the primary end point was evaluation of an intervention targeted at changing altering EF (e.g., inotropes) or if patients had known myocardial dysfunction. Case reports and case series were also excluded. A standard form was used to extract the relevant data based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [15]. When data on specific endpoints were not available, authors were contacted and the information requested. Publication bias was not assessed, as traditional tools like the funnel plot can be misleading when applied to diagnostic data [16]. Study validity was assessed based on the Standards for Reporting of Diagnostic Accuracy Initiative and the Review of Methodological Standards [17].

2.2. Data abstraction

Three researchers (RSB, JO and VV) independently screened the studies from the search described above. Data were abstracted using a standardized form. Disagreements were resolved by discussion. Variables abstracted included study description, population studied, degree of heart failure, cause of sepsis, severity of illness, and mortality. Low EF was defined by the individual studies, with 6 studies using a cutoff of 50% [4,18–22] and 1 study using a cutoff of 45% [23]. For the purposes of evaluating low EF as a prognostic measure of mortality, study outcomes were classified as patients with ventricular dysfunction who died (true positive [TP]), patients with ventricular dysfunction who survived (false positive [FP]), those without myocardial dysfunction who survived, (true negative, [TN]), and those without myocardial dysfunction who died (false negative, [FN]) were abstracted as well. Sensitivity [TP/(TP + FN)] and specificity [TN/(TN + FP)] of myocardial dysfunction for predicting mortality in sepsis were subsequently calculated. Positive likelihood ratio [LR^+ = sensitivity/(1 − specificity)] and negative likelihood ratio [LR^- = (1 − sensitivity)/specificity)] are used to evaluate how a study measure influences posttest probability using Bayes theorem. For a positive test result, pretest probability × LR^+ = posttest probability; and a negative test pretest probability × LR^- = posttest probability. The effect that a test has on posttest probability can be summarized by the *diagnostic odds ratio* (DOR), defined as LR^+/LR^-, where higher values denote a better discriminatory diagnostic test [24].

Sensitivity and specificity are true performance statistics for a test independent of disease prevalence in a population. The major determinant for these values is the cutoff differentiates positive from negative tests, for example, the degree of dysfunction at which a patient is diagnosed with ventricular failure at a particular institution. A high cutoff will have a low false0positive rate (high specificity) but will also miss more cases (low sensitivity), whereas a low cutoff will have the opposite effect. This cutoff value is termed the *diagnostic threshold*.

2.3. Statistical analysis

Sensitivity and specificity and the reference standard were calculated from the data in each study. Pooled sensitivity, specificity, LR^+, LR^-, and DOR were calculated for heart failure with the use of the DerSimonian-Laird random effects model [25]. For each statistic, the 95% confidence intervals (CIs) were calculated based on the F distribution method for the binomial proportion [25].

An assessment of heterogeneity was performed with the use of I^2 analysis, where 0% indicates low heterogeneity and 100% high discordance between studies [26]. Subgroup analyses were conducted using meta-regression to determine what contribution individual factors such as prevalence and definition of sepsis have on heterogeneity, where P values <.05 indicate a contribution to heterogeneity. One source of heterogeneity unique to diagnostic meta-analysis is the threshold effect, which occurs when studies implicitly or explicitly use different thresholds to define a positive test result. The presence of threshold effect is tested by calculating the Spearman coefficient between sensitivity and specificity, where values ≤0.5 or >0.5 indicate possible threshold effect [27].

A summary measure of accuracy (Q*) was calculated, which corresponds to the upper leftmost point on the summary receiver operating characteristic (SROC) curve, where sensitivity equals specificity. This value can be between 0 and 1, with 1indicating the highest sensitivity/specificity. This value has been recommended over the area under the receiver operating characteristic curve region of greatest interest [28,29]. Statistics were calculated manually and with use of Meta-DiSc software [30].

3. Results

3.1. Literature search

The database search yielded 1504 records; and manual inspection of references, an additional 1 article. Nine hundred seventy-six articles remained after removing duplicates. All abstracts were screened; and of these, 156 were deemed potentially relevant, and full text was obtained. Of these, 143 were excluded for addressing different end points, animal studies, and pediatric cases, leaving 15 articles for inclusion in qualitative synthesis. Seven of these articles contained sufficient information to proceed with quantitative review and meta-analysis. This study strategy is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Fig. 1).

3.2. Study description

A detail description of each of the 7 included studies is provided in the Table. All studies were prospective observational studies on ICUs. Six studies were in patients with severe sepsis and/or septic shock. One study was on septic events on cancer patients [23]. The total combined population was 585 patients. Most studies contained small study population with a median of 51, and 2 studies accounted for 53% of the overall cohort (337/585). All the studies were single-center studies, 2 of them in United States [4,21], 3 in Europe [18,20,23], 1 in China [22], and 1 in Australia [19].

Three studies used serologic markers as prognostic factors on septic patients with LV systolic dysfunction and also had a TTE within 24 hours of ICU admission evaluation during their protocol [18,19,23]; meanwhile, the rest of the studies evaluated the use of TTE as the

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